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Human Adaptation to the Parasitic Environment.

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ABSTRACT.—Man, in contact with the pathogens in his environment, responds by developing immunity with or without symptomatic illness. The incidence of infectious disease in a community depends on the parasitic factor or "infection pressure," and the host factor, "herd immunity," i.e., the resistance of the community as a whole to the infection. Environment is only a secondary factor which alters the relative values of the two primary factors. Morbidity varies directly as the "infection pressure," and inversely as the "herd immunity." The great difficulty heretofore has been to separate the two factors expressing morbidity. In diphtheria, to some extent, this is now possible by means of the Schick test. By using clues gained from the study of diphtheria, and examining the age-incidence, severity, and fatality, of other infections under various environmental conditions, the hypothesis is reached that herd-immunity increases with the herd's past experience of the bacterial causes of most, if not all, infectious diseases. This immunity may be acquired latently, without illness, and, even if not always enough to prevent symptomatic infection, may be such that severity and fatality are decreased. The process is an example of the general biological mechanism by which the members of a species acquire adaptative variations more suitable to the environment. Of recent years air-borne droplet infections have caused less fatality and trouble to the English herd than a century ago. The manifold increase of the density and of the motion in the English herd must have greatly raised the average infection-pressure, but since severity of clinical disease has diminished and incidence has not increased in proportion, the herd-immunity of the English must have outstripped the increase of infection-pressure, i.e., the herd has become more closely adapted to its bacterial environment. It must not, however, be forgotten that adaptive fluctuations in parasitic characters must also play some part in all the phenomena of infectious disease.

ADAPTATION is a word which means the same thing whether in small talk or in a biological discussion. A man may be well or badly adapted to his job, an animal to its environment, a host to his parasites, or *vice versa*.

When competition is slack animals can hold their environments in spite of considerable maladjustment; but if the struggle for existence is keen the man will be eliminated from his job, and the dependent organism will get "sacked" by its host, should they not be closely enough adapted to the niche they occupy in the world. The environment may change and a previously well-adapted organism find that it cannot exist under the new conditions. On the other hand another animal may vary readily in response to all the changes in its surroundings, and succeed where a more specialized organism would fail. The power of adaptability is called plasticity, and it is one of the most valuable biological qualities a species can possess. Men and bacteria are both most plastic organisms, and this largely accounts for their pre-eminence and ubiquity.

The free-living bacteria and the great majority of the specific parasites of other animals are innocuous to man, who destroys any who get in his way. Others are harmless commensals which man tolerates, since they cause him no inconvenience. The group of dependent organisms which concern medical men are the potential pathogens. These parasites are imperfectly adapted to their hosts, and have the power of causing those unpleasant reactions called disease. In some members of this group the mutual adjustment between man and microbe is all but complete. For example, the meningococcus usually causes a symptomless infection, or at most an unnoticed catarrh of the naso-pharynx, and meningitis is only a rare complication. Individuals who, though infected with potential pathogens, give no reaction marked enough to attract attention are the so-called carriers of disease. In the Navy I estimated that there were at least 3,000 carriers of *agglutinable* meningococci

to every case of epidemic meningitis. In other conditions, such as smallpox, clinical signs and symptoms are the usual accompaniment of infection. Between these two types there are many others, such as scarlet fever, where typical and atypical clinical cases and symptomless carrier infections are all common. Thus, according to circumstances, the same parasite may initiate a fatal, severe, mild, or carrier infection. Such divergent host reactions were commonly explained by variations in parasitic virulence. But many observations suggest that variable host resistance is the more usual explanation of the severity gradient of clinical symptoms which is to be seen in all epidemics. I strongly emphasize that fluctuations in the parasitic characters concerned with virulence and infectivity must, in the long run, be as important fundamental factors in epidemiological phenomena as host resistance. However, in most of the hypotheses formulated to explain the relationships between host and parasite, variable dosage of infective material can be used as a substitute for variable virulence. Therefore, to simplify the discussion I shall assume that we are dealing with that biological *chimera*, an immutable, rigid, parasitic species.

On this assumption there are two direct causes of the severity gradient from carrier to fatal infection—the dose of the infective agent and the resistance of the host to microbic invasion. In the same person, if the dose is too small to cause illness, it may be large enough to cause symptomless infection, or the carrier state, while still smaller doses may be destroyed, even before they begin to multiply in their host. With the same dose of infective material the receiver's degree of resistance will determine whether he destroys them or becomes infected as a carrier or case. A certain amount of immunity, or rather a power of rapid response to microbic stimuli, which is plasticity, may be a genetic quality, and inheritable in the strict sense, but human resistance to infection is more often than not acquired during life. The resistance to microbic attack will depend on how often the subject has been infected as a case or carrier, or on how many bacteria he has destroyed in the past, and the distribution of this bacterial experience in time. In infants and young children resistance depends also on the mother's history. This congenital, as distinct from true hereditary, immunity, is a remarkable adaptation to the bacterial environment. The baby is born with a ready-made immunity to the parasites it will find in its new environment, which is, of course, the same as that to which its mother is already adapted. This immunity is a passive one, but it tides the infant over its first few months until it can begin collecting an active immunity of its own. Congenital immunity is more common than was realized before the Schick test showed that a new-born infant practically always had the same immunity reaction as its mother. The newly-born mammal may also imbibe immunity with its mother's milk. The work of Theobald Smith and Little [1] is very striking in this respect. They found that eight out of twelve calves who received no colostrum from the cow died from *Bacillus coli* septicæmia within a few days of birth, whereas ten controls, removed after only fifteen minutes' suckling, survived. Owing to the difference in the anatomy of the placenta in cows and goats, maternal antibodies are chiefly transmitted in the milk, whereas, in rodents and man, maternal immunity is usually conveyed by way of the umbilical vessels. However, human milk also often contains diphtheria antitoxin, and Peter's [2] exhaustive analysis of epidemic diarrhœa suggests that human milk may contain immunizing substances against the agents which cause this infection.

To summarize: immunity to bacterial invasion is acquired by a visible attack of ill-health, or more frequently invisibly, by the following: latent sub-clinical infection, or the carrier state, auto-vaccination with living bacteria in the food or atmosphere, or possibly even by ingestion of dead bacteria, or their products, in the dust, as well as by passive transference of maternal antibodies by way of the placenta or in milk.

I will now consider the community, or the herd. The herd may be large or small, with many subdivisions or smaller herds. Nations may be divided into urban or rural herds, or we can contrast the shore-going herd with the sailor herd, or herds dwelling in hospitals can be compared with those who live in mental hospitals. In epidemiology, herd pathology, or medical ecology, the concept of resistance to the spread of infectious disease in the herd is not exactly the same thing as the sum of the resistance of its individual members. For example, if it were possible to measure resistance by titrating the antitoxin content of the blood of all the members of the herd, it might be found that, in a community of one hundred, there were fifty who had one unit of antitoxin per c.c., and fifty who had none. In a second group of one hundred, each member might have 0·1 unit of antitoxin. In the first herd the average resistance would be equivalent to 0·5 units per c.c. per head, fivefold that in the second herd. Yet all field observations go to prove that the first herd, with a large number of completely susceptible members, would be more liable to an epidemic than the second, where everybody had some resistance.

The term "herd-immunity" was, I believe, invented by Topley [3], who thus defines it: "The resistance of the herd at any given moment will be determined by the frequency distribution within it of individuals of varying orders of susceptibility." This definition refers neither to the environment nor to the density of, and motion in, the herd, and, as I use the term, it is not intended to do so. However, having heard Professor Topley on this subject since the delivery of his Milroy Lectures, I think he does include environmental factors in his concept of herd-immunity. In one sense the resistance of the herd to microbic attack varies with the position and movement of its members relative to each other, but I find it more convenient, and a seemingly more accurate description of fact, to consider such external factors as density of, or movement in, the herd not as directly affecting immunity, but as influencing the intensity, rate of distribution, and reception of infection. For example, when soldiers sleep in a hut so close together, and for so long at a time, that meningococci can cross the gap between one soldier and another in sufficient numbers to cause meningitis, the change in the environment has increased the duration and rate of distribution of infection beyond that existing outside the hut. Therefore the resistance to the spread of meningitis is less in the hut than outside it, but according to my concept, the herd-immunity of the group of soldiers was not instantaneously lowered when they entered their sleeping quarters. Herd-immunity, in this paper, only describes the fundamental host factor, irrespective of the environment. For want of a better name I shall call the fundamental parasitic factor "infection pressure," which is determined by the frequency distribution of the various rates at which infective material is being received by the members of the herd (variable "virulence" may also be included).

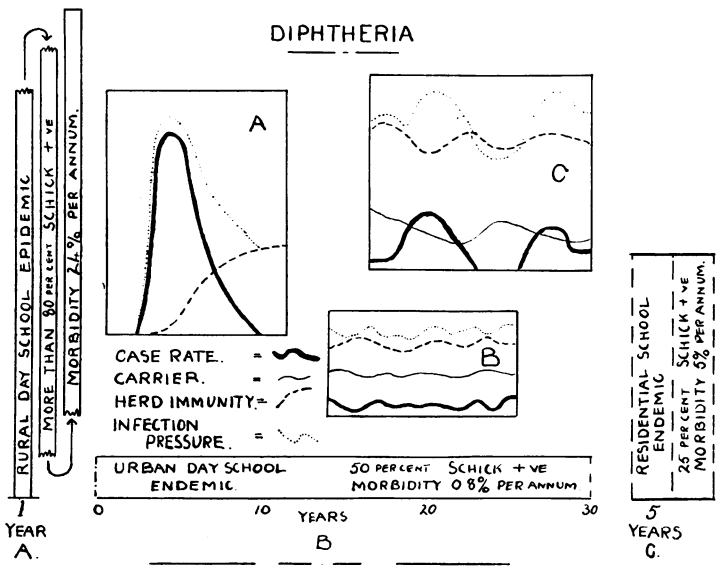
Infection pressure and herd-immunity react on each other. Increase of infection pressure is followed by a rise in the herd-immunity, which in turn retards, stops, and may ultimately decrease infection pressure to zero. A zero infection pressure means that the pathogenic virus has disappeared or relapsed into a harmless commensal. In this event the herd immunity falls to its minimum at a rate which, according to the nature of the infecting parasite, may require either a few weeks, or long enough to replace the whole population. In other cases the infection pressure does not fall to zero, but it and the herd-immunity attain an unstable equilibrium, the varying periods and amplitudes which are reflected in the incidence curves of endemic, sporadic, and seasonal disease.

The values, and differential value, of these fundamental factors, herd-immunity and infection-pressure, determine the type, quantity, rate of spread of infection, and the relative frequency and distribution of fatal, severe, mild, and symptomless cases in the herd. Environment is a secondary cause, it cannot produce disease in the absence of either host or parasite, but this does not mean it is not as important

a factor in determining the amount and type of herd infection. Environment includes all such secondary factors as atmospheric conditions, motion, density, and customs of the herd, which act directly on infection pressure; and nutritional changes, chill, and fatigue, which may temporarily, or permanently, modify the herd-immunity.

Fig. 1 represents these concepts diagrammatically. The rectangles and diagrams A, B, and C, refer to three school herds. A, a rural day school in New Zealand. B, the L.C.C. day schools, and C, Greenwich Hospital School. The vertical heights of these areas are proportional to the diphtheria morbidity and their bases proportional to the time taken for a number equivalent to 24 per cent. of the average population to contract diphtheria. Therefore, these areas are equal, and represent the same relative amounts of morbidity spread over different periods. The social class and age-groups of the three herds are comparable. The school environment of A and B are roughly similar. The environment of C differs in that the inhabitants

FIG 1.

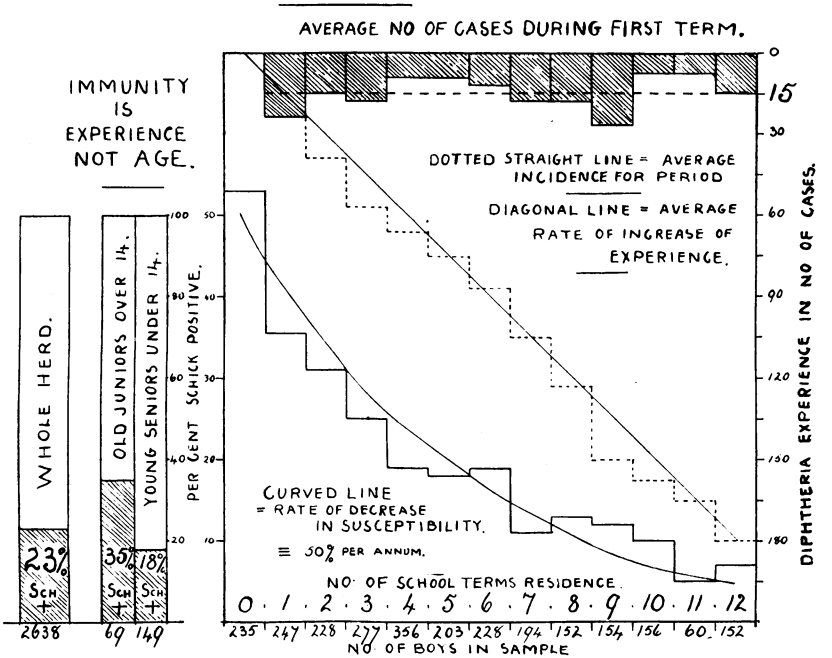


HERD IMMUNITY * INFECTION PRESSURE * ENVIRONMENT.

spend the night sleeping one hundred or more close together in one room (the mean age of this herd is also greater). A had been free from diphtheria for some years when the infection was introduced. Diagram A is supposed to explain what happened. The infection pressure at once rose steeply, unchecked by herd-immunity, which was at a minimum. After a preliminary lag the herd-immunity began to rise. The increase in infection pressure was retarded, and then declined to meet the rising herd-immunity, when infection vanished and the epidemic was over. I assume in these diagrams that the level at which herd-immunity is drawn is such that when infection pressure falls below this level symptomatic cases can no longer occur. Morbidity is thus made to represent the difference between infection pressure and herd-immunity. The thick continuous lines which are merely diagrammatic and are drawn to no scale envisage the attack-rate of clinical diphtheria. In fact, in these diagrams the infection-pressure curve is the ordinary incidence curve, using the maginary curve of herd-immunity as the base line. A, for simplicity's sake, may

be taken to represent an epidemic on virgin soil, which runs a rapid course, and finishes owing to the virus dying out. The epidemic cannot recur until the herd-immunity has subsided to a suitable level and infection is re-introduced. In B and C diphtheria has become endemic. In B it required fifteen years to accumulate as much diphtheria morbidity as the New Zealand epidemic produced in six months. The curves for infection pressure, herd-immunity, and morbidity in environment B tend to maintain the same relative levels and only oscillate within small limits determined by environmental factors. C shows the same thing, but the morbidity is less regular, herd-immunity is higher than in B, but owing to the environment (a residential school), the infection pressure is relatively higher still, as is indicated by the greater average distance between it and herd-immunity which is reflected in the higher morbidity. The herd-immunity level is drawn with regard to symptomatic

FIG. 2



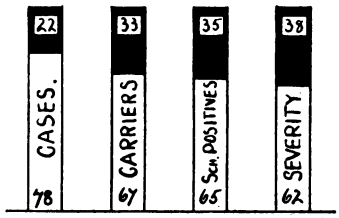
clinical infection, therefore carrier infection can continue even when the infective pressure has dropped below that value of herd-immunity at which clinical cases cease to appear. In diagram C this has been indicated by the gap in the case-incidence curve, without any corresponding break in the thin line which represents carrier incidence.

In diphtheria, intensive use of the Schick test, in combination with other clinical and laboratory observations, has given a clue to the solution of some general problems in the spread of infection. The Schick test has been so useful, because in it we have a simple reliable method of measuring the relative immunity of herds irrespective of infection pressure. Fig. 2 embodies some of the more interesting results of my work on this subject. The wide column on the left shows the average percentage of Schick positive reactors in the whole herd at Greenwich Hospital School during nine years.

In the diagram this herd has been broken up into thirteen groups of boys arranged according to the number of terms they had been in residence at school before being Schick tested. Zero represents new entries to the school, and twelve boys who had twelve terms (i.e. four years) at school. The bottom flight of steps represents the percentage of Schick-positive reactors in these samples. The upper flight of inverted steps gives the average number of cases of diphtheria notified during the residence of the corresponding sample below. The diagram shows clearly that, as experience of diphtheria increased, susceptibility declined. The shaded rectangles indicate the average number of cases occurring in the corresponding terms. The dotted line indicates the average number of cases per term for all terms, which was fifteen. The diagonal line represents the accumulation of this experience if it has been evenly distributed throughout the nine years to which these figures relate. Similarly the curved line indicates the decline in susceptibility, from 50 per cent. to 5 per cent. of positive reactors, if it had occurred evenly at a rate equivalent to 19 per cent. of all susceptibles per term. The expected closely follows the actual decline. In case it might still be thought that this increase in herd-immunity is a physiological function of age occurring irrespective of bacterial experience, two columns are given

FIG 3.

DIPHTHERIA.



DURATION OF EXPERIENCE	AVERAGE POPULATION OF GROUP	6 YEARS DIPH CASES	MORBIDITY % PER ANN	CARRIERS FOUND IN ONE TERM	CARRIER RATE %	SCHICK + PER CENT	RATIO CASES TO CARRIERS
UNDER A YEAR	280	129	7·7	56	20	36	(2·3)
OVER A YEAR	720	94	2·2	69	10	10	(1·4)
TOTAL	1000	223	3·6	125	13	23	(1·8)

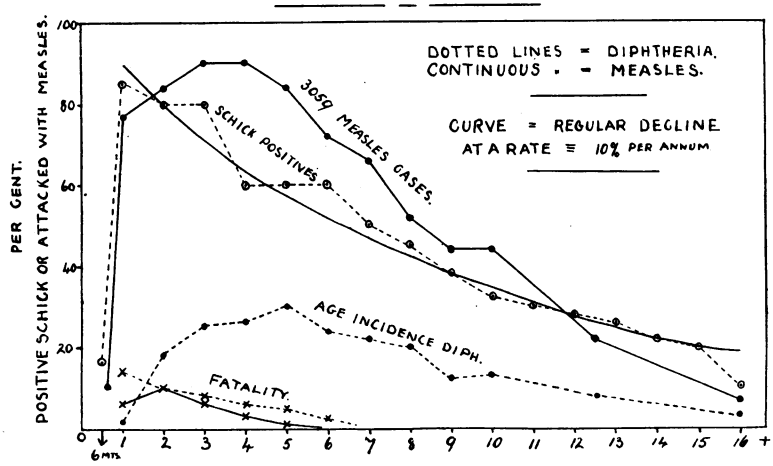
MORBIDITY * IMMUNITY * SEVERITY.

representing the proportion of Schick-positive reactors in two groups of boys tested at the same time. One set were all over fourteen, but had been less than a year in school, all the others were under fourteen, but had had over a year's experience of the school environment. The junior group, though older, contain relatively twice as many susceptible reactors as the younger, but senior, group. It is fair to conclude from these observations that immunity to diphtheria is an acquired adaptation to the diphtheria bacilli in the environment, which, far more often than not, is produced without any unpleasant reaction in those places where diphtheria is endemic. In Greenwich Hospital School about three boys became immune while one acquired clinical diphtheria. This ratio is probably lower than usual owing to the exceptionally high infection pressure of this special environment. According to Frost [4], the ordinary urban environment of Baltimore produces seven latent immunizations to each case of clinical diphtheria.

Fig. 3 gives a table in which the same herd has been split into two groups, the one with under, and the other with over, a year's experience of this high diphtheria infection pressure. The frequency distribution of cases, carriers, and Schick positive reactors, is given in the table, the last column of which shows the ratio of clinical diphtheria cases to carriers. The carrier figures were obtained from a single experimental swabbing of the whole school (1,000 boys) in order to avoid the errors due to the ever-changing carrier-rate. Because the carrier is only the limiting clinical case, the ratio of cases to carriers can be used as an index of severity of infection. The four columns above the table demonstrate the relative frequency of cases, carriers, and positive Schick reactions in the junior and senior sub-herds, when the number of each class in the whole herd is reduced to one hundred. The relative severity of infection in the two groups is suggested by a fourth column, which envisages the relative magnitudes of the case-carrier ratios. The senior group only contains about a quarter of the cases and one-third the relative amount of severity,

FIG 4.

DIPHTHERIA AND MEASLES



UPPERMOST CURVE = INCIDENCE AMONG CONTACTS WITH NO HISTORY OF MEASLES.

LATENT IMMUNISATION IN MEASLES.

carriers, and Schick-positive reactors, found among boys of under a year's experience. Hence in diphtheria, provided the environmental conditions remain the same, morbidity, carrier-rate, and the case carrier-ratio can all be used as an index of herd-immunity since all decline in harmony with Schick susceptibility.

Fig. 4 compares latent immunization in measles and diphtheria. I will first deal with the dotted lines which refer to diphtheria. The uppermost dotted line is an age-incidence curve of positive Schick tests in the Berlin population [5]. After the rapid loss of congenital immunity during the first year of life, the susceptibility, as measured by Schick testing, drops from 85 per cent. to 20 per cent. in fourteen years. This implies an average rate of immunization equivalent to about 10 per cent. per year of the susceptible population, as shown by the smooth continuous curve. The corresponding rate in the Greenwich residential school was over 50 per cent. per annum, due to the high infection pressure in the dormitories. Therefore using this rate of immunization as a measure of infection pressure, the pressure in the school was fivefold that of an ordinary town environment. The age-incidence group for

clinical diphtheria does not follow the decline in Schick susceptibility until the fifth year of life is reached. This increase in morbidity up to five can be explained by supposing the chances of infectious contacts to become greater as the developing infant increases in mobility, reaching a maximum when the child begins school life. It must ever be borne in mind that morbidity depends on both herd-immunity and infection pressure, whereas Schick test statistics depend on herd-immunity only.

The main object of fig. 4 (p. 31) is to demonstrate that latent immunization also occurs in measles. When in 1922 [6] I first wrote on latent immunization in diphtheria, measles was instanced as a disease in which immunity was only gained by actual attack. Since then I have carefully re-read the brilliant paper on measles which Butler [7] read at this Section in 1913. Butler noted that the number of contacts who escaped attack in measles could not be entirely explained by immunity due to previous attack, or by escape from all contact with the virus. He observed that the attack-rate among those in houses who were in contact with measles, but who had no past history of measles themselves, decreased regularly with age, i.e. susceptibility to measles declined with age, irrespective of a clinical attack of measles. The continuous lines in fig. 4 show a graph made from Butler's tables of the measles attack-rates in Willesden among house contacts who gave no past history of measles. This measles curve has been superimposed on the Schick-test curve in order to show how the decline in measles susceptibility closely follows the decline in susceptibility to diphtheria toxin. Note how the congenital immunity for measles and diphtheria both rapidly disappear during the first year of life. But the measles curve, which is a morbidity curve, and therefore depends also on infection pressure, does not definitely decline until the fourth year of life. This may either be a real immunity phenomenon, as loss of maternal immunity is slowly compensated for by increasing gains in active immunity, or it may have an explanation similar to that suggested to explain the age-incidence of clinical diphtheria, namely that an increase in infection pressure due to the change in environment as the child herd grows from one to five, has masked a real increase in herd-immunity. The curve of the Willesden children is confirmed by Butler's other observations on the escape of contacts at Marlborough College. 30 per cent. of the boys had no past history of measles against 10 per cent. of the similar age-group at Willesden; but at Marlborough only 17 per cent. of the boys escaped attack as against 82 per cent. of the poorer group. This suggests that, as in diphtheria, the poorer social group had acquired more immunity than the protected well-to-do one. This hypothesis is probably correct in part only since the contrast in measles morbidity between Marlborough and Willesden may have been caused by the environmental difference between a residential and day school. For example, in a reasonably long period (10 years), the boys of the naval school suffered ten times the diphtheria morbidity as boys in the same age-group (12-16) and social class in London day schools. Halliday's [8] recent analysis of the measles incidence in Glasgow tenements confirms Butler's deduction that latent immunity, without obvious clinical attack, does occur in measles. Thus in 1913, when Schick and Michiels published their original paper on the cutaneous immunity reaction for diphtheria, Butler was able to conclude from the vital statistics of measles that . . . . . "Not age, *per se*, but the opportunity it confers of acquiring an active immunity through exposure to attenuated or minor doses of infection brings about the changes in susceptibility exhibited in the table" (fig. 4).

Before leaving fig. 4, notice that severity as indicated by case-fatality also falls with susceptibility, but, without knowledge of all the details, case fatality may be a deceptive guide to immunity, because specific fatality is often exaggerated, by secondary infections: witness the malign partnership between the streptococcus and the diphtheria parasite at present causing anxiety on the Continent.

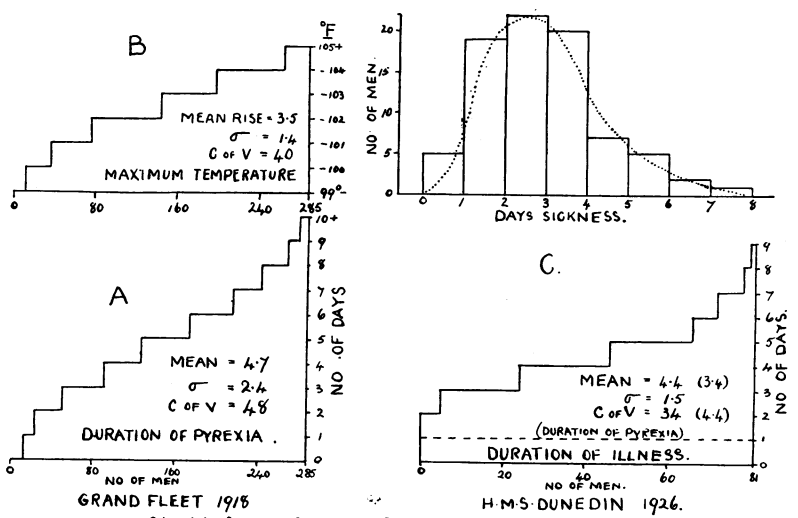
The recent English report [9] on vaccination, and that by Force [10] in America, state that many subjects with no past history of smallpox, or previous vaccination,

give an immediate reaction to vaccinia virus, which indicates immunity to smallpox. The popular explanation is that these immunes, owing the present mildness of smallpox or alastrim, are missed cases. Except on academic grounds, these men have acquired their immunity latently, since they were not ill enough to complain, or to attract the attention of others; hence the effect of their presence in the population on herd-immunity, and the spread of disease, is the same, whether they are called missed cases or carriers.

The difference in latent immunization in measles and diphtheria is, that whereas in the former the immunity acquired is generally sufficient to prevent subsequent clinical attack, in measles it only has a very small effect on susceptibility to ultimate attack, but a great effect on fatality and severity of infection, i.e., as susceptibility declines, the herd moves down the gradient in severity of clinical symptoms. I will try to explain what the severity gradient is, by the help of figures 5 and 6 (pp. 33, 35) made from data of influenza epidemics in ships. To measure the exact clinical severity

FIG 5.

EPIDEMIC INFLUENZA.



CLINICAL SEVERITY - GRADIENT.

of an illness is impossible, but rise of temperature, though not entirely satisfactory, is roughly related to the intensity of the uncomplicated reaction to the influenza virus. The diagrams A and B (fig. 5) refer to 285 patients that I diagnosed in 1918 as uncomplicated influenza. In B these men are arranged in order of duration of pyrexia. In diagram A they are grouped according to the maximum rise recorded on their temperature charts. Both sets of steps show a good range of variation. This series came from many ships in the Grand Fleet at a time when all sorts of secondary organisms were forming parasitic complexes with the influenza virus. This variability was as likely to have been due to variations in the infecting agents and environments as to immunity differences. Therefore I made diagram C from a series of 81 cases from one ship who comprised the total patients in one small epidemic, which produced no complications of any kind. My notes of this outbreak only gave the number of days each man was on the sick list, but since almost, without exception, I discharged each man to duty directly his temperature had been

normal for twenty-four hours, the mean duration of pyrexia was one day less than the duration of illness. Diagram C is arranged both as a set of steps and as a frequency polygon, and shows a range of variation quite comparable to A and B. This variability seemed more likely to be caused by some host factor rather than by variable parasitic dosage.

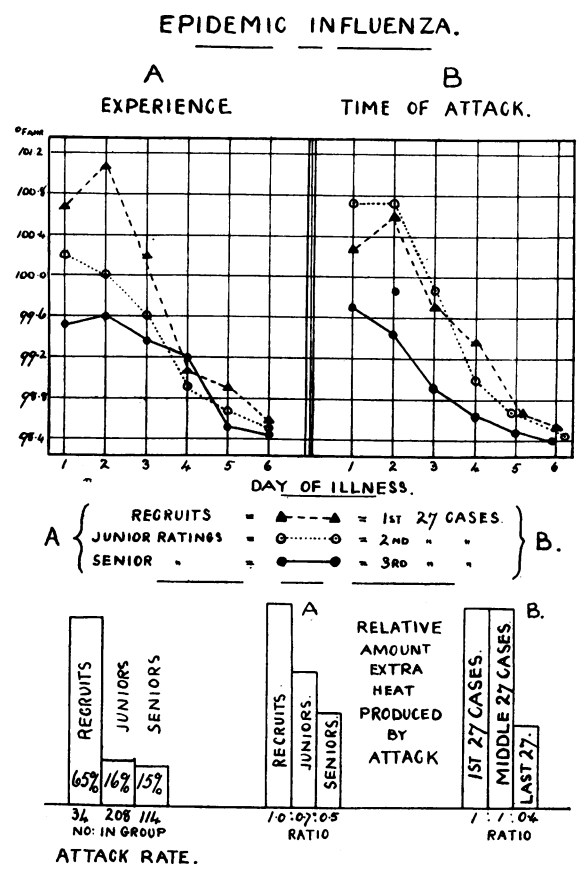
To compare the relative severity of infection in different sub-divisions of the herd, temperatures were averaged, thus making a herd temperature chart [11]. Fig. 6 gives some of these charts. In chart A the eighty-one cases are divided into three groups: recruits, junior trained men, and petty officers (senior trained men). The attack-rates of these three classes were 65 per cent., 16 per cent., and 15 per cent. respectively, making evident the lower herd immunity of the recruits; but there was no indication that the petty officers, in spite of having been longer at sea, had more resistance than the junior trained men. If, however, the herd temperature charts of these three groups are examined, the degree of pyrexia varies inversely as the experience of the herd, and the senior trained men are seen to have produced definitely less extra heat than the junior group. Thus, although senior were as susceptible to initial attack as junior trained men, yet, once attacked, the seniors escaped with a less severe illness, as is indicated by their lower average temperature. Brownlee [13] by comparing the morbidity among the vaccinated and unvaccinated demonstrated exactly the same herd-immunity phenomenon in smallpox. Twenty-five years after vaccination, immunity to attack is no greater in the vaccinated than in the unvaccinated, but the protection against death and severe illness persists throughout life. Thus the herd-immunity of two groups with differing past histories, subjected to the same infection pressure, may permit the same amount of initial infection in each, but the severity of the illness will be less in the group with the most bacterial experience. This phenomenon is parallel to that demonstrated by Glenny [12] for diphtheria toxin and other antigens. Though an animal may have no toxin in its blood, yet, if it has had previous experience of toxin, antitoxin will appear rapidly in response to the stimulus of a dose of toxin so small as to produce no effect in an animal which has not had a primary stimulus or experience of diphtheria toxin. Glenny has shown that "this principle of increased power to respond" is almost a general law as regards antigen-antibody reactions in experimental animals. Probably the same immunological mechanism is at the bottom of the phenomenon in herd pathology just described.

The temperature graphs in B (fig. 6), illustrate another fairly common observation. The eighty-one influenza patients were divided into the 1st, 2nd and 3rd twenty-seven men who reported sick during this epidemic. The first two batches have almost identical herd-temperature charts, but the last twenty-seven cases were very mild and produced only half as much extra heat per man as the first fifty-four. The mildness of the terminal cases in an epidemic can be explained thus: The outbreak starts off with a rush, and the infective pressure rises rapidly before herd-immunity can develop. In the middle period herd-immunity rises, but the infection pressure is now at its maximum, and the difference between pressure and resistance remains too great to allow clinical severity to subside, until the final stages of the epidemic, when infection pressure is rapidly waning, while herd-immunity is still rising. The terminal cases of an epidemic, although they have not resistance enough to avoid attack, yet have acquired enough experience of the infecting agent, during the earlier stages of the outbreak, to limit the average severity of their illness, i.e., severity is another index of closeness of adaptation between the herd and its potential pathogens. Since no line can be drawn between the mildest case and a contact carrier, diphtheria also illustrates very well the diminution of severity as the herd-immunity rises towards the end of an epidemic. At a time when the incidence of clinical diphtheria in a herd had almost dropped to zero, experimental throat swabbing showed that the carrier-rate for virulent bacilli had actually gone up.

Therefore the epidemic was still in progress, but no longer visible: "mild," or symptomless, had replaced "severe," or symptomatic, infection. In such a case the infection pressure may have remained as high as ever, but the severity of infection had been swamped by the rising herd-immunity.

The case-carrier ratio as an index of herd-immunity can only be used where the environments are similar. For instance, the average carrier-rate over seven years was roughly the same (about 5 per cent.) in both Greenwich Hospital School and

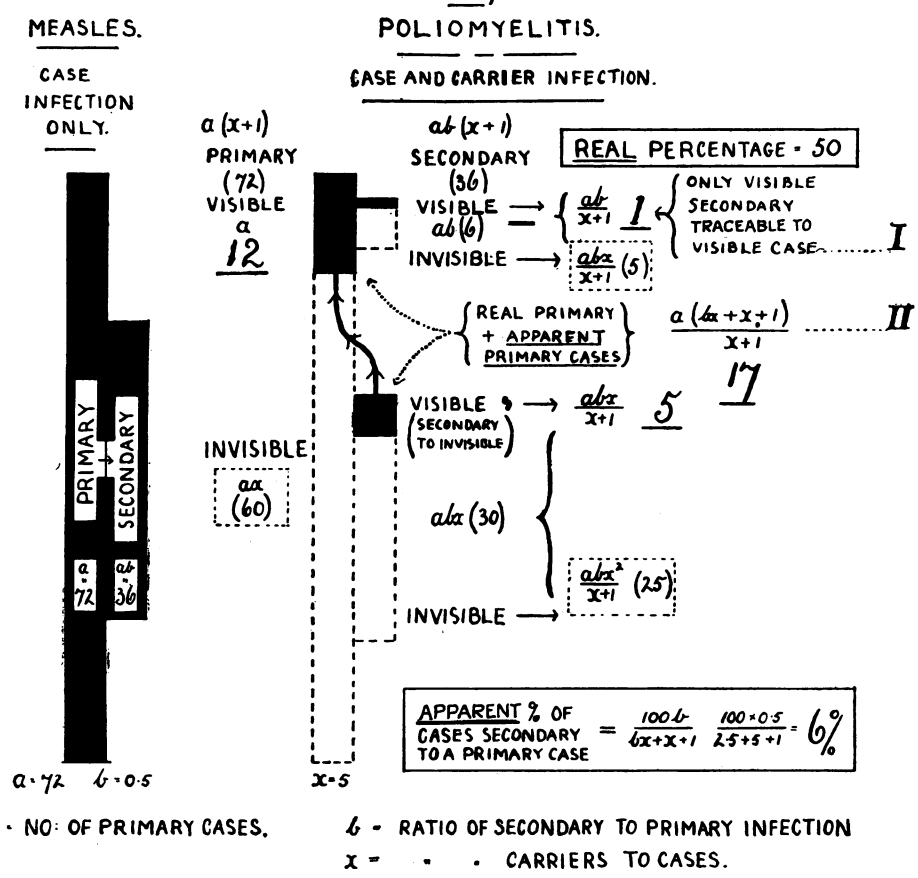
FIG. 6.



the L.C.C. day schools, but the case-rate was five times as heavy in the residential establishment. Therefore the case-carrier ratio was also five times as great in the Naval school as in the London schools. In the absence of other data, this observation might suggest that the immunity of the Naval herd was less than that of the London schoolboys. However, Schick-testing showed that the herd-immunity in the naval residential establishment was always much greater than among the London school children. Although the herd-immunity was high, infection pressure

was relatively higher and outweighed any tendency of the herd-immunity to reduce the severity of infection or the relatively high case-carrier ratio seen in residential as compared with day schools. The effect of herd-immunity in altering the ratio between cases and carriers is best exemplified by the epidemiology of poliomyelitis. Before investigating this let us examine briefly the effect of carrier infection on certain morbidity statistics. Aycock and Peaton [14] suggested that infantile paralysis and measles may have different methods of dissemination as there

FIG 7.



EFFECT OF CARRIERS ON MORBIDITY STATISTICS.

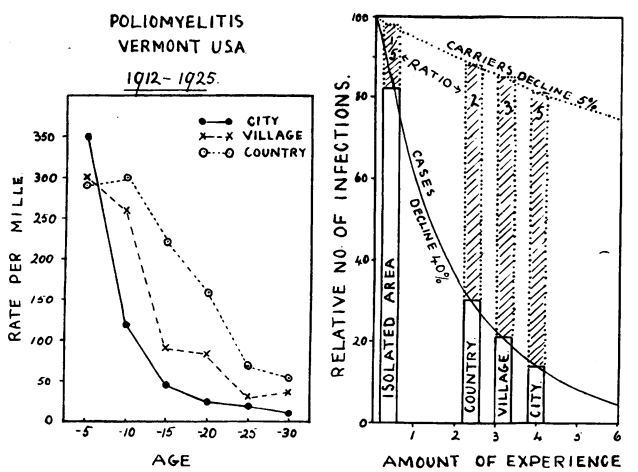
is a great contrast between the two diseases in the frequency with which secondary infections follow a primary one in the same family. These authors gave statistics which showed that about 50 per cent. of primary measles cases were followed by a secondary infection, whereas for infantile paralysis this percentage was only 4·3.

The diagram shown in fig. 7 is an attempt to explain the apparent low rate of secondary infections in poliomyelitis, or any other infection which produces carriers as well as cases. For the purpose of explanation, it is assumed that all infections

with the measles virus are visible cases, and that the distribution of the virus of poliomyelitis is *exactly* similar to that of measles, except that five out of every six infections are invisible carriers. In measles, 108 infections appear as 72 primary followed by 36 secondary cases. In poliomyelitis 108 infections would only show as 17 primary cases and one secondary case, because only 12 out of 72 primary infections are visible. These 12 cases are followed by six secondary infections of which only one is a visible case. The other 60 invisible infections produce 30 secondary infections, of which only five are visible cases, since the primary infections producing them were all invisible carriers. These five cases, which are really secondary, will be classed with the 12 real primary cases in the notification returns. Thus the apparent percentage is 6 per cent., while the real percentage of secondary infection is 50 per cent. just as in measles. Fig. 7 also gives a general equation for any proportion of primary and secondary cases, and any ratio of carriers

FIG 8.

DECLINE OF SUSCEPTIBILITY TO CASE AND CARRIER INFECTION



INCREASE OF CARRIER-CASE RATIO WITH HERD IMMUNITY

to cases. If the figures of Aycock and Peaton are substituted in this formula, the value of the carrier- to case-ratio would be seven for New York. Another set of measles and infantile paralysis statistics makes carriers 42 times as numerous as cases. As little or nothing is known of the relative infectivity and herd-immunity of measles and poliomyelitis, the algebra in fig. 7 has no practical significance, and was only introduced to emphasize a principle which explains why there is sometimes great difficulty in tracing infection from one symptomatic case to another; and also to show that there is no necessity to assume that the means of dissemination of the virus of poliomyelitis is essentially different from that of measles, just because so few families report a second case of infantile paralysis.

Returning to the thesis that herd-immunity alters the ratio of cases to carriers: fig. 8 is modified from some statistics in another recent paper by Aycock [15].

During a reasonable period (12 years) it is seen that the total incidence of clinical infantile paralysis is greater in the country than in town. It is scarcely conceivable that the virus, if it spreads by droplet infection, can be disseminated more easily n the country than the town. The obvious explanation is that carriers are in a larger ratio to cases in town than in country, and therefore the total infections with the virus of poliomyelitis are just as high or higher in the town. The age-incidence in the town drops more quickly than in the country, suggesting a higher average, or less intermittent infection pressure in town than country, which implies that there is, if a sufficient period is considered, a greater average density of infectious foci in town than country. But as fig. 8 shows, infantile paralysis is more common in the country, therefore the surplus of infections in the town must be symptomless carriers. In the United States poliomyelitis infection becomes more irregular and intermittent as it passes from the town, to village, to country, but intermigration is so extensive as never to let the virus disappear for very long at a time, hence herd-immunity can never fall as low as it may do when the virus disappears for long periods, as happens in certain remote villages of Sweden, the Pacific islands, and even in exceptional spots in England. To prove a rule, examine the apparent exceptions. Reece [16] reports that in Stoke Rivers, an isolated Devonshire village, 14 houses out of 18 were infected in 40 days; 11 houses returned multiple cases. The total morbidity of symptomatic poliomyelitis was 30 per cent. of the 119 inhabitants. The attack-rate for infantile paralysis in Stoke Rivers was 120 times that of Vermont district, U.S.A. for 12 years. In Stoke Rivers multiple cases in one house were 20 times as frequent as in New York. Again, in Stoke Rivers the infection was probably most often direct from case to case, and carriers were not common; because, even if it is assumed that everybody who escaped symptomatic infection was a carrier, the ratio of carriers to cases could not have been more than 2 : 1 in Stoke Rivers, whereas in New York, on the most conservative estimate, this ratio must have been over 7, and, in my opinion, was probably nearer 100. The possibility that epidemics of infantile paralysis where multiple cases occur in one family, and the general attack-rate is high, are due to massive doses of the virus in milk must not be overlooked. For example Aycock [17] has suggested that milk was the vehicle of infection in the Broadstairs outbreak [18], where about 7 per cent. of the inmates of certain private schools contracted symptomatic poliomyelitis. But, even if both Broadstairs and Stoke Rivers were infected by milk, the difference between incidences of 7 per cent. and 30 per cent., especially when we consider how easily disease spreads in residential schools, indicates that the herd-immunity of the private schools was much higher than that of the isolated village, therefore the hyopothesis that the case-carrier ratio is higher in rural than urban districts still holds good. I do not think either outbreak had anything to do with milk. Reports of poliomyelitis outbreaks, such as those at Dennington and Grays [19], suggest that in rural districts the tracking of infection from case to case is often easy; and the "carrier hypothesis" in unnecessary. In contrast, the M.O.H. of a great town like Leicester [19], reports 82 cases, with little evidence of any connexion between them, and states that the 19 school children who were attacked with infantile paralysis in Leicester were attending 16 schools.

The diagram in fig. 8 tries to envisage the relation between carrier and case infection and herd immunity. The heights of the unshaded portions of the columns represent the relative morbidity of symptomatic infections. The heights of the three unshaded columns on the right are proportional to the total morbidity in the country, villages and towns of Vermont, U.S.A. The numbers along the base line represent the relative intensity of the stimuli from the virus of polio-myelitis each of these herds is imagined to have had. The susceptibility of the herd-to-case infection declines with the experience, as shown by the lower curve. The susceptibility to carrier infection is presumed to decline much more

slowly, as suggested by the dotted upper curve. Therefore the relative number of carrier infections corresponding to any intensity of experience will be represented by the vertical distance between these two curves, which represent the rate at which immunity is acquired to case and carrier infection respectively. In the selected examples the relative incidence of carrier infections is represented by the dotted and shaded parts of the columns. The column on the left-hand side of the diagram may be taken to represent a place like Stoke Rivers, which had had no experience of the virus before being attacked. In this column the difference between the curves as drawn would indicate that the herd-immunity was such that only one carrier would occur to every five cases; whereas in the column marked "city," the number of carriers to cases would be in the inverse ratio of 5:1. This diagram may also be used to envisage an ideal age-incidence curve. The first column would then represent young unsalted children, who tended to become cases more often than carriers, and the column labelled "city" would correspond to seasoned adults, in which carrier, rather than case, infection was the rule. It is also of interest to compare this hypothetical diagram with the three real age-incidence graphs, in fig. 8, which show nicely the different rates at which susceptibility declines in three herds of decreasing experience. Thus, the hypothesis of a variable case-carrier ratio can explain a good deal in the epidemiology of infantile paralysis. The case carrier-ratio is another index of the degree of adaptation of the herd to the parasitic environment.

Before leaving the subject of poliomyelitis, I should like to say that variations in the functional characters of the virus probably play an important part in its epidemiology.

I will now try to show that the herd can acquire a considerable immunity to even such a trivial and ubiquitous infection as the "common cold." In such a vague recurrent syndrome, the clinical and bacteriological correlations of which are not yet understood, and in which the issue is so complicated by auto-infection and short-period fluctuations in herd-immunity, secondary to temperature and other environmental factors, it is useless to expect evidence of increased resistance by finding a complete absence of attack, subsequent to the first cold. But if a census were made of all the colds suffered by each member of the herd, during a fixed period, and if it were discovered that the frequency of attack diminished as experience increased, provided that allowance could be made for environmental factors, it would be good evidence that the herd did acquire immunity to the common cold. Such evidence is contained in a report on the minor respiratory diseases, issued by the U.S.A. Public Health Service [20]. In this investigation the heads of 775 families, comprising 2,498 individuals (1,203 ♂, 1,295 ♀) reported all the "colds" in their families during one year. This population produced 3,794 "colds in the head and nose." Fig. 9 (p. 40) is made from data supplied in the report. The continuous line in the figure represents the frequency of male, the dotted line that of female "colds" at different age-periods. The frequency of colds in males falls to a minimum between the ages of 15 to 24; because during home, school and college life resistance is increased with age and bacterial experience; but some time, between the ages of 25 and 34, the male cold again becomes common, as though the herd-immunity gained in early life had been lost. This *apparent* loss of resistance was disconcerting, until the character of the population under examination was realized. The heads of the families, who each reported for his own household, were mostly medical men in the public services, and therefore the majority of the males, between 25 and 34 years old, must have been young husbands, or even elder sons, starting the practice of their profession. Many of these males, especially those in the fighting services, would be continually coming into contact with the minor droplet infections, and thus run a greatly increased risk of catching colds. The sudden rise in the curve was therefore due, not to loss of immunity, but to the increased

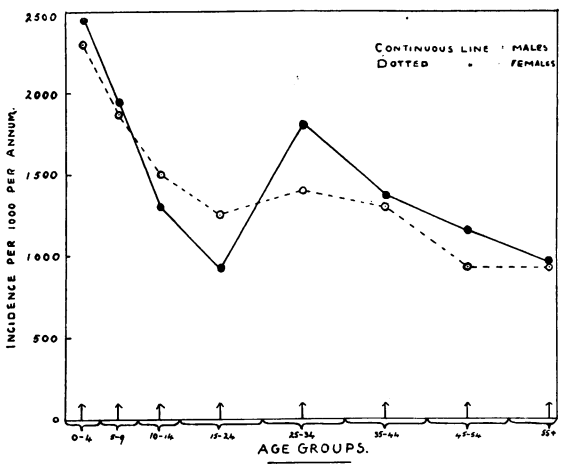
infection pressure inseparable from medical and service life. As adaptation to the new environment was slowly developed, the frequency of colds again diminished.

If these inferences are correct, the young professional men who caught cold must often have carried the infection to their homes, and a similar check in the decline of colds should be seen in the female incidence curve. However, because the relative number of males and females of the same age in each family would be approximately similar, the check in the female curve should be spread over a longer period, i.e., the female curve should show the same oscillations as the male, but considerably smoothed out—and it does.

Let us consider a simple case. Two husbands, in the 25 to 34 age-group, catch cold and infect their wives. One wife is the same age as her husband, the other one is 20 years of age and therefore in the younger group of 15 to 24. The result of these infections will be to increase two of the female age-groups by one. At the same time

Fig. 9.

"COLDS" U.S.A.



HERD IMMUNITY IN MINOR DROPLET INFECTIONS

the one male group will be increased by two, while the other remains unaltered. The total of similar infections introduced into the home will cause the relative number of 15-24 male colds to be less, and the 25-34 infections to be greater, than the corresponding numbers for female colds, as is clearly demonstrated in fig. 1 (p. 28) by the difference between the male and female incidence curves.

In small isolated communities, such as ships or islands, colds often disappear when the herd breaks contact with civilization for any length of time, only to reappear when contact is made again. Either the infection dies out in the intervals, or the closely intermingled members of the herd soon adapt themselves to each others' commensal flora. I found an interesting example of this type of phenomenon in Boswell's "Life of Johnson" [17]. Boswell relates how Johnson criticized Macaulay for offering as true, the absurd story that whenever a ship arrived at St. Kilda, a small island in the outer Hebrides, all the inhabitants at once caught cold. Subsequently, Johnson apologized for the criticism, because he had meanwhile

learned from a Dr. Campbell that the story was a well attested fact, and that the inhabitants of St. Kilda caught cold because they were unaccustomed to the "effluvia from the human bodies of strangers." Boswell, while he admits the fact, can scarcely swallow the explanation. However, a Mr. Christian wrote to Boswell, expressing his surprise that a man of Dr. Johnson's acumen should have missed the real cause of the St. Kilda colds. There was no mystery at all, because, owing to the situation of the harbour, no vessel can approach the island except when the wind is in the nor'-east; and anyone knows that north-east winds and colds are cause and effect. In view of van Loghem's [22] recent paper on the effect of temperature changes on the incidence of colds, Mr. Christian may have been correct, but, nevertheless, I favour Dr. Campbell's explanation of the St. Kilda colds and would merely substitute "infected droplets" for the word "effluvia." A modern confirmation of Boswell's story is of interest. In June, 1913, H.M.S. *Active* was ordered to steam at once to the assistance of the inhabitants of St. Kilda, who had been stricken with a mysterious disease. Surgeon Captain Hall [23], then medical officer in H.M.S. *Active*, notes that for nine months of the year St. Kilda has no communication with the outer world, and even in the summer the swell is frequently so great as to make landing impossible. He then states that on June 12 a tourist steamer anchored at dawn in St. Kilda harbour, sailing again at noon. This steamer was boarded by many of the islanders; within twelve hours of the ship's arrival a few individuals were already complaining of symptoms. (A shortening of the incubation period seems to be another indication of low herd-immunity.) Within five days the whole population of St. Kilda, except six elderly people, were suffering from a complaint with the following symptoms: sudden onset, great prostration, temperatures up to 104° F., acute post-orbital pain, aching in all limbs, irritable cough, and no definite physical signs; the duration of the illness was generally less than a week. In fact they showed one of the most typical of the many clinical pictures of uncomplicated epidemic influenza.

In 1913 the virus of influenza introduced by some stranger caused a 92 per cent. attack-rate in the inhabitants of a completely unsalted island. This rate is higher than any I have heard of, even among densely packed herds which occupy men-of-war. Therefore, in 1913, influenza could strike down a whole herd whose immunity was at a minimum, yet it required five years of war, with its commingling of nations, before the virus acquired sufficient potency, or a high enough infection pressure, to swamp the herd-immunity of the whole world. In St. Kilda everyone gets a cold at once; the herd-immunity rises at once to a relatively high level, and the infective agent is either eliminated or becomes avirulent. Herd-immunity to colds, being of a most transitory nature, then drops rapidly to a minimum so that the next time the virus is introduced the islanders all catch cold together once more. Since these paragraphs were written Heinbecker and Irvine Jones [24] published an investigation which shows that the behaviour of minor respiratory infections among polar Eskimos (probably the most isolated race in the world) is an exact replica of Boswell's story of St. Kilda. Immunity to colds requires constant stimuli to maintain, hence the St. Kilda cycle is only a short-period example of a long-period phenomenon; this can be seen in an infection like measles which confers life-long immunity. Take for example the two classical epidemics in Fiji. The Fijians had never heard of measles before 1875, when the virus found a population with no herd-immunity and caused a morbidity estimated at 100 per cent. of 100,000 population with a 25 per cent. fatality. After the epidemic the virus disappeared and the herd-immunity was absolute. As new members were born and old ones died, the herd became sharply divided into two distinct classes: the absolutely immune and the completely susceptible. For some years all infants would be born with a transitory congenital immunity to measles, but after thirty years even congenital immunity would be getting scarce and more than half the Fijian population would have had no

measles experience. Time would be ripe for another disaster. In 1907, 40 per cent. of the population acquired measles, and the fatality was estimated to be also about 40 per cent.

Although these morbidity figures are crude estimates, it is fair to conclude that though the morbidity was halved, the fatality in 1907 could have been no less, even if it was not nearly double, that of 1875. This is exactly what was to have been expected if the herd was divided sharply into immunes and susceptibles. The Fijian experience indicates clearly that herd-resistance is not the same thing as the summed resistance of the individual members. Such a disaster as happened in 1907 could not occur in London, where nearly everyone has a little experience of measles before he is ever attacked by it. Notwithstanding, it is conceivable that the sum of the resistance of an average hundred Londoners might be less than that of one hundred average Fijians just before the 1907 epidemic. If, for the sake of explanation, complete herd-immunity is envisaged as black, and full susceptibility as white, and the population is represented as a strip from birth to death. Before 1875, the Fijian strip was pure white from end to end; immediately after the first epidemic it became wholly black. Then (congenital immunity being omitted for simplification) one end of the strip would rapidly become a pure white sharply divided from the black; and as time went on, the line, dividing white from black, would travel along the population strip towards old age, until the second epidemic arrived and painted the whole strip once more black. In contrast to Fiji, in a city where measles is ever present, the population strip would never be pure white or black. Typically it would be dark grey at birth, due to transmitted maternal immunity. Then, after rapidly fading to a very light grey, the shade would slowly deepen to nearly black as adult life was approached. In other types of environment, such as country places with variable degrees of traffic with the outer world, in which the visitations of an infectious virus are irregular and intermittent, the population strip might be painted in almost any arrangement of black, grey and white bands, in any order, width, or depth of shading.

Schick test graphs, of herds arranged according to age, often give indications of these imaginary bands in the varying slopes of the curve. Special environments of a stable character tend to balance their herd-immunity and infection pressure at a specific level. The introduction of recruits of lower herd-immunity than the original inhabitants causes a fall in the immunity of the newly constituted herd, followed at once by a rise of infection pressure. The incidence of symptomatic infection is thus augmented, not only in the more susceptible recruits but also in the original inhabitants, who succumb to the increased pressure of infection. This phenomenon has been shown experimentally, in a herd of mice, by Greenwood, Topley, and their collaborators [25] and perhaps explains the very high incidence of infectious disease in schools, recruiting depots, and any other place where the inexperienced are mixed with those who have become closer adapted to their parasitic environment.

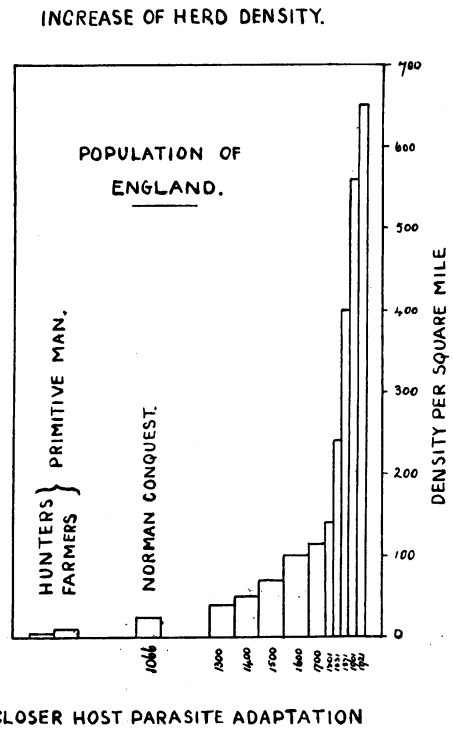
Many good examples of the adaptation of the herd to its parasites may be found among protozoal, and even helminthic, infestations, but I have confined my illustrations to droplet infections only; because none can claim that, up to the present, intelligent human interference can have done much to disturb the natural relations between man and the air-borne bacteria, as is the case with those dependent organisms which travel from host to host in food, water, or other vehicles.

Adaptation to the parasitic environment may also be effected by a true natural genetic immunity, as opposed to acquired natural immunity. In this respect Hirszfeld's [26] concept that natural anti-bodies may be inherited as ready-made "serum structures" or "biochemical organs" is of speculative interest.

Moreover, I must mention non-specific acquired herd-immunity and susceptibility: How far does experience of one variety of parasite alter the herd-resistance to others?

Just as it was found that the augmentation of immunity following artificial bacterial vaccination was an imitation of a natural process, so it follows that the numerous test-tube experiments, which show all sorts of cross-and-group immunity reactions, also imitate processes which occur in Nature. Hamer's well-known demonstrations of the sequence of epidemics in a definite cycle is of great speculative interest in this respect; they suggest that the experience of one complex of organisms paves the way for another. If so, Hamer's [27] epidemic sequences are perhaps another example of ecological succession, such as is seen after a forest fire, when an orderly sequence of plant communities follow each other, as the forest slowly returns to its pre-fire condition. On a smaller scale the ecological succession of bacterial species can be

FIG 10.



seen in a test-tube of an infusion of fæces, or other material, as Topley [28] and other biologists have demonstrated. The bacterial flora in the test-tube changes in a definite order as the environment varies, and may be, bacterial communities, when living in their normal habitat, the herd, follow similar laws. I have had no time to discuss important secondary factors, such as weather. However, Sir Leonard Rogers [29] has dealt exhaustively, and scientifically, with the effect of atmospheric conditions on the spread of many important diseases, such as cholera, plague, leprosy, and small-pox. Perhaps climate and weather have bulked so largely in epidemiology, to the exclusion of more fundamental factors, because the action of weather is so marked

in diseases transmitted by an insect vector. Gill's [30] work in the Punjab clearly shows the pre-eminent importance of weather in the herd-pathology of plague and malaria. These diseases were almost synonyms for fever to the ancients, and malaria was rampant in classical Greece and Rome. Hence Hippocrates and his followers were naturally impressed by the weather, since malaria follows the seasons, can be blown away by a wind, or become a malignant epidemic after a flood.

My concluding diagram (fig. 10, p. 43) is modified from one by C. Saunders [31], and shows the density of the population of England throughout the ages. Primitive hunting man was a beast of prey, and, like other wild animals, must have been much more closely adapted to his environment than modern man. The struggle to avoid elimination was so severe that it is unlikely that sickness and malignant parasites could survive for long in prehistoric times. As man passed into the agricultural and historic period, the margin of safety separating the human species from elimination widened, and there was more room for the malignant parasite. Inter-communication was nothing like it is to-day, and more or less isolated tribes probably attained a fair degree of temporary equilibrum with their own parasitic environments; a balance which was continually upset whenever intermingling of the herds took place, such as in war. The conjunction of war and pestilence in history is significant. As the diagram shows, the population of agricultural England increases very slowly to the end of the eighteenth century. Then, suddenly, the rate of increase becomes so greatly accelerated that in one century the density is increased sixfold. This increase, due to the industrial era, is really greater than the diagram indicates, as the population is now concentrated into the relatively minute areas of the big towns. Intermigration and contacts between different herds have increased relatively even more than density. This continuous mixing of the population implies a continuous interchange of parasites, by which a very effective balance is maintained between infection pressure and herd-immunity. During the last century the expectation of life has increased, the fatality and severity of practically all common infectious diseases have declined, and morbidity has shown no increase commensurate with that of the compression, multiplication and activities of the population.

As Rolleston [32] and Chapin [33] have pointed out, marked changes have occurred in the clinical characters of disease. Are we to attribute all these recent variations in man's host-parasite relationships entirely to improved public health measures, or to admit that a part of the improvement is due to closer adaptation between man and microbes? Over twenty years ago Ray Lankester [34] noted "that unless further evidence should prove him wrong, the adjustment of organisms to their surroundings was so severely complete that disease is probably unknown as a constant and normal phenomenon; and recently Dean Inge [35] stated, with no qualification, that wild animals are "completely adjusted to their surroundings." Wild animals are by no means as closely adapted to their environment as was once believed, and even epidemics are a normal and constant periodic phenomenon in the life histories of many species.

The following sequence of events, as given by Elton [36], is most instructive. Every eleven years solar activity is at a maximum and causes the average temperature of the earth to go up 0·6 degree. The extra heat, in turn, produces an increase in vegetation, as is proved by the periodic fluctuations in the width of the annular rings of the giant pines of California. More plant life means more food for many animals, including the varying hare of North America, which, as a result, increases its fertility from 5 to 6, to 8 to 10, young per litter. The resulting increase in numbers now places the hare beyond the control of its natural enemies or checks—the fox and lynx. These animals, since they are slower breeders than their prey, cannot multiply fast enough to eat up all the surplus hares. Once out of control the hares multiply more and more rapidly until the increase is terminated by an epidemic of disease, which wipes out all but a few of the more resistant animals, and another eleven-year cycle commences.

Thus a cosmic cause, the sun, acts, through the weather and food-supply, on the environment of an animal and allows it to multiply far beyond the control of its normal biological checks. An increase in infection pressure or some other alteration in the host-parasite relationship, which is thus produced, in turn stimulates a usually harmless commensal to escape the control of its host, and become a malignant pathogen. The result is an extensive epidemic which restores the balance of numbers, of both host and parasite, to where they were eleven years previously.

It is interesting to note that Wayson [37] in describing the causative microbes of similar epidemics in field mice, is unable to determine definitely the systematic position of these bacteria because "the virulence is subject to such vagaries." England is perhaps fairly safe from a big disaster due to one of the common pathogens in their present form, but there is ever the possibility of some new mutant, or variety of the bacteria, arising in response to the ever-increasing density and motion of modern herds, and wiping out the excess population, as happens periodically with the varying hare. This would not be altogether undesirable, as the density of the English herd must be already well beyond the optimum. Dependent organisms must vary in response to the stimulus of the environment, just as their hosts do, but the parasitic characters on which virulence and infectivity depend are vague, elusive, and difficult of measurement, even in the controlled and unnatural surroundings of the laboratory, so that at present it is not possible to learn much about the adaptative fluctuations that must take place in the natural environments of parasites—their specific hosts. I conclude, therefore, by emphasizing once more that to describe adequately the phenomena of herd pathology, parasitic adaptation to the human environment is no less important than its antithesis, human adaptation to the parasitic environment.

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DISCUSSION.

Professor W. W. TOPLEY said it was a great encouragement to those who were attempting to study the genesis and progress of epidemics under relatively simple experimental conditions, to hear Commander Dudley's account of careful and prolonged observations, carried out on human herds. With regard to the particular question of herd-immunity, it seemed desirable to include in this category two different types of increased resistance, both dependent on the structure of the herd as such. They might reasonably regard any herd as immune to

a particular infection, if it was so constituted that the introduction of a focus of that infection was not followed by any spread among the members of the herd. Herd-immunity, as so defined, might be divided into two main types : (*a*) That in which the immunity was dependent on the distribution of resistance, innate or acquired, among the individuals composing the herd, and (*b*) that in which the immunity was determined by environmental factors—for instance, by the absence of some insect vector of infection. It was, of course, the former type with which Commander Dudley had been mainly concerned, and which had occupied the attention of Professor Greenwood and himself in their experimental work. One of the greatest merits of such studies as those of Commander Dudley seemed to him to be that they afforded an example of the study of infective disease as a biological, rather than as a purely clinical phenomenon. By studies along such lines as these, it was probable that they should one day be able to discuss the phenomena which had been recorded by Sydenham and his followers, in terms of the reactions between parasite and host, which had been studied in the laboratory and in the field.

Sir WILLIAM HAMER said there was good reason for thinking that Sydenham had in mind a *specific*, not a non-specific, interaction between germ and host, and the paper on "The Influenzal Constitution," to which Surgeon Commander Dudley referred, had as its text a sentence of Sydenham (M.O. I., i, 6), which, it was claimed, "might be regarded as a first attempt at formulating the fundamental concept of immunology. Sydenham and Willis both realized, 250 years ago, "That there were infecting particles and a disposition of the blood and humours to react when acted upon by them. There was an interplay of conflicting forces and constitutions were thus engendered." In this interplay, or interaction, parts would (nowadays) be allotted doubtless not only to the host and the specific germ, but also, in Surgeon Commander Dudley's phrase, to any "usually harmless commensals" which might chance to be stimulated into "malignant pathogens." Thus "the sequence of epidemics in a definite cycle," so carefully described by Sydenham, represented much more than mere ecological succession"; his successive writings displayed to view two almost complete cycles of changes (1658-1675 and 1675-1688), and, when the phases of influenza thus exhibited were fully envisaged, it became difficult to refrain from concluding that specific changes, primarily due to interaction between a germ and its host, were in question. If it were objected, why not regard the pandemic influenzas as forest fires and all the rest as "ecological sequence," the reply was that it could not be done, for the simple reason that the view adumbrated by Sydenham, Willis and their followers had, during the last half century, been amply confirmed by Creighton and his disciples, by official reports coming from Whitehall, and by a number of witnesses from abroad. The fire, in fact, was ever smouldering, though it was only at intervals of from ten to twenty years that it burst into flame. The key to the mystery was that, as Sydenham had it, while the fever "sometimes attacked the bowels, sometimes the head," and might cause great prevalence of coughs and catarrhs, it was "the same fever throughout, . . . all the diseases which had originated from it had been the same."

Professor M. GREENWOOD said that Surgeon Commander Dudley's work was of first-rate importance. Nobody else having similar opportunities had had the patience or the sagacity to make precise observations of the changing epidemiological constitution of a human herd. Whatever they might think of Surgeon Commander Dudley's interpretations—and certainly he had amply earned the right to frame hypotheses—they must be of one mind as to the value of his exact observations. One must try to imagine what happened within a herd defined in the simplest terms and then seek to test one's hypothesis against the observed facts. He supposed the simplest case was that of a herd receiving no new members during the period of observation but subjected to a steady bombardment of "infection." One might suppose that "shots" were fired at random, so that some individuals were never hit during the period of observation, some were hit once, some twice, and so on. One must then suppose that the fact of being hit an assigned number of times determined in some a clinical illness, in others an enhancement of resistance. How the constitution of the herd, in respect of the proportions of members of it becoming (*a*) "cases," (*b*) "carriers," (*c*) "immunes," changed with time had to be determined. They must restrict themselves to a "law" the parameters of which were not too numerous to be determined from the data. Even in this simplest case of a closed herd there were great difficulties of description to be conquered; when the herd accepted immigrants the difficulties increased. But they must

and should conquer these difficulties in time as data accumulated. He hoped that Surgeon Commander Dudley's example would stimulate others with similar opportunities to take up this fascinating branch of research.

Dr. R. A. O'BRIEN appealed to Surgeon Commander Dudley to extend his work to influenza and the common cold. He considered the present position with regard to these two diseases as the greatest reproach to modern medicine, for the available methods of research had not been used. In the case of yellow fever Reed and Lazear showed that volunteers could be obtained for infection with deadly diseases, and the Laidlaw-Dunkin work emphasized how important it was to be sure that the experimental animals should be unquestionably susceptible to the disease under investigation. Proper inquiries into influenza and the common cold would need the support of large funds and, most of all, the help of suitable volunteers who would undergo the necessary isolation for considerable periods and the subsequent infection experiments with filtrates, etc. But they might end up by finding that there was a long series of filterable viruses causing common colds. And here knowledge was lacking. Did the cold, with sore throat, cough and tracheitis breed true, and did it produce immunity? Did the cold with sneezing and nasal catarrh produce it? He (the speaker) begged Commander Dudley to make records of his boys. He hoped the medical officers or matrons of isolated preparatory schools in the country would also make fully detailed daily records of every boy. From these we might begin to get some accurate knowledge about common colds.

Dr. A. JOE said that he was not sure that the inherited immunity in measles was such a definite phenomenon as that seen in diphtheria, since children at very early ages succumbed to the first chance of exposure. He also said that, since the point had been raised by Professor Topley, as far as clinical observation could show there was no evidence of an infective carrier state in measles.

Professor S. LYLE CUMMINS said that it was interesting to find that Surgeon Commander Dudley had not confined his statistical studies to morbidity and Schick tests, but had also taken into account the "severity" rates, as estimated in terms of temperature and "stays in hospital." He (Professor Cummins) thought that modifications in severity in the course of epidemics of given diseases had not been sufficiently studied in their bearing upon the immunological side of epidemiology. He suggested that Commander Dudley would find many facts to support his hypothesis of "herd immunity" in the study of modifications of clinical types, and also of pathological characters in contrasted sections of human populations in chronic diseases, such, for instance, as tuberculosis.

Surgeon Commander S. F. DUDLEY (in reply) said he was glad Professor Topley was in agreement with him in emphasizing the fact that all medical problems were problems in biology. In order to be an epidemiologist, in other words a medical ecologist, one had to be a "Jack-of-all-trades," and as a result master of none. All the "masters,' especially those whose trade was pure biology, must turn their attention to human herd pathology, and lend a hand to "Jack" if they wished to accelerate progress in medical science. Sir William Hamer's objection to describing "the sequence of epidemics in a definite cycle" as an ecological phenomenon was, perhaps, due to a misunderstanding. Ecology was only a "shorthand" expression for the study of the mutual reactions between different kinds of living matter and environments. The ecological succession of epidemics was only a clumsy attempt to translate Sir William's next phrase into general biological terms, and neither explained nor contradicted anything Sydenham ever said. Professor Greenwood's warning concerning the complexity of the subject was timely, but it was hoped that the few simple hypotheses put forward would not be taken as evidence that he (the speaker) imagined that the behaviour of epidemic disease had been adequately described by them. These hypotheses, better termed "suggestions," were only made to be refuted or modified by fresh facts. Dr. O'Brien might like to know that a large amount of time had been expended in studying the distribution and incidence of minor respiratory disease at Greenwich, but with little result. But, as Dr. O'Brien pointed out, this work, especially the technical bacteriology concerned, required more labour and time than one man, even without other duties, could find for it. The answers to the questions raised by Dr. O'Brien were of such paramount importance to the health of the human species that it was to be hoped the time was not far distant when

someone, with the control of the necessary funds, would realize this was a fact. The support of Professor Cummins on the significance of the severity gradient in epidemic disease was most encouraging. Severity was as important as morbidity, considering that 100 men sick for three days and three men sick for 100 days was a fair description of some outbreaks of so-called "influenza." As Dr. Joe, remarked there was no evidence that active carrier infection existed in measles. Nevertheless there were observations which showed that immunity could be acquired irrespective of clinical attack. How it was acquired was unknown, perhaps by the absorption and immediate destruction of subinfective doses of the virus.